Remarks

A Request for Continued Examination (RCE) and the required fee for the RCE are enclosed.

The Office Action mailed May 11, 2007, has been received and reviewed. Reconsideration and withdrawal of the rejections are respectfully requested.

Since the last office action, this application has been licensed. The licensee is a small entity. The licensee has requested that a number of additional claims, i.e., claims 32-47, that were not included in the original filing because the assignee, a university, did not have funds to prosecute these claims, be added with this RCE. Further, claims 13-17 have been replaced with new claims 20-31 to more succinctly specify the invention. Therefore, the pending claims are claims 1-9 and 20-47.

Claim Objection

The Examiner objected to claim 13 alleging the following informalities: in the step of the claim beginning "removing the complexes of new bacteriophage and second substrate" it appears that the claim should read - - removing the second substrate comprising immobilized binding agent for the new bacteriophage, to which the new bacteriophage, if present, is complexed - -, and that the following step should read not on the detection of the complexes generally, but on the detection of new bacteriophage on the second substrate. Claim 13 has been replaced by the new claim 23, which includes the same language as the original claim 13 but has been made dependent on new claim 22 for efficiency of claiming. Applicants respectfully disagree.

Applicants submit that the claim is clear to one skilled in the art and, therefore, that no change is required.

The 35 U.S.C. §103 Rejections

Claims 1-4, 6, and 9 are patentable over Rees *et al.* in view of Miller *et al.*

Claims 1-4, 6, and 9 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Rees *et al.* (WO 92/02633, hereinafter "Rees") in view of Miller *et al.* (WO 01/09370 - as translated in U.S. 2002/0127547, hereinafter "Miller"). This rejection is respectfully traversed.

MPEP § 2143 states that in order to establish a *prima facie* case of obviousness, three basic criteria must be met:

> (i) there must be a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
>
> (ii) there must be a reasonable expectation of success; and
>
> (iii) the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Applicants respectfully submit that the Office Action fails to set forth a *prima facie* case of obviousness because, at least, the combination of Rees and Miller ("the suggested combination") fails to set forth each and every feature recited in claim 1. Moreover, one skilled in the art would have had no motivation to combine the documents as suggested in the Office Action.

Claim 1 is independent. Each of claims 2-4, 6, and 9 depends, directly or indirectly, from claim 1. Thus, remarks that refer to claim 1 apply equally to claims 2-4, 6, and 9. Claim 1 recites a method of detecting a bacterial cell in a sample. The method includes, in part:

> contacting the sample with bacteriophage comprising a binding agent, wherein the bacteriophage is specific to the bacterial cell and wherein the bacteriophage comprising a binding agent is immobilized on a substrate;
>
> incubating the sample under conditions effective for the bacteriophage

> comprising a binding agent to infect the bacterial cell, and if a bacterial cell is present in the sample and has been infected by the bacteriophage comprising a binding agent, form new bacteriophage and release new bacteriophage into the sample, wherein the new bacteriophage do not comprise a binding agent;
>
> removing the bacteriophage comprising a binding agent immobilized on a substrate from the sample; and
>
> detecting new bacteriophage in the sample from which bacteriophage comprising a binding agent immobilized on a substrate have been removed, wherein the presence of new bacteriophage indicates the presence of a bacterial cell specific for the bacteriophage in the sample and wherein the absence of new bacteriophage indicates the absence of a bacterial cell specific for the bacteriophage in the sample.

Applicants respectfully submit that the combination of documents fails to set forth all of the features recited in claim 1. Specifically, the suggested combination fails to set forth removing immobilized bacteriophage from the sample that is subjected to a detection assay.

Rees teaches detecting bacteria by allowing bacteriophage specific for a target bacterium to infect target bacteria if present in a sample. Extracellular bacteriophage are killed without killing phage-infected bacteria. The infected bacterial cells produce progeny phage, which may be detected by various methods. The Office Action acknowledges that Rees fails to set forth immobilizing the parent phage and removing the parent phage after progeny phage are released by the infected bacteria (Office Action, page 4).

The Office Action states that Miller teaches that when a sample is contacted with an immobilized phage, "there is no stringent necessity to remove such from the sample prior to detection." (Office Action, page 4). The Office Action concludes that Miller therefore teaches that immobilized phage may be removed at any point after infection of the target bacteria in the sample. Applicants respectfully disagree with the characterization of Miller provided in the Office Action. Further, Applicants submit that Miller fails to teach or suggest removal of immobilized phage at all.

The cited paragraph ([0026]) of Miller reads, in its entirety:

> If the sample contacted with the immobilized phages or phage proteins, e.g., in a flow-through chamber or on a filter, there is no stringent necessity to remove it after binding the bacteria to the phages or phage proteins prior to carrying out the detection.

Applicants respectfully submit that this paragraph does not refer to removing immobilized phage from the material subjected to a detection assay, but refers to removing unbound material in the sample from the portion of the sample bound to immobilized phages or phage proteins. This interpretation is supported in paragraph [0011] of Miller, which reads, in part, "...subsequent to the step of specific cell recognition and subsequent to the separation of unspecifically bound bacteria a corresponding binding assay is performed[.]", the Abstract, and the claims (the Abstract and claims reading, "..optionally removing the sample and the bacteria in the sample not bound to the bacteriophages and/or bacteriophage proteins,"). In contrast, the interpretation advanced by the Office Action finds no support anywhere else in Miller.

Thus, the immobilized phage in Miller remains *with* the material on which the detection assay is performed—the bacterial cell bound to the phage/phage proteins. In contrast, claim 1 recites *removing* the immobilized phage *from* the material being detected—the progeny phage. Thus, contrary to the position set forth in the Office Action, Miller fails to teach or suggest removing immobilized phage from the material subjected to the detection assay.

Because Miller fails to teach or suggest removing immobilized phage from the material subjected to the detection assay, Miller fails to cure the deficiencies of Rees acknowledged in the Office Action. Consequently, the combination of Rees and Miller fail to set forth all of the features recited in claim 1. Thus, the Office Action fails to establish a proper *prima facie* case of obviousness. Applicants respectfully request that the rejection be withdrawn.

Applicants further respectfully submit that one skilled in the art would have had no motivation to combine the documents as suggested in the Office Action. Rees detects bacteria by allowing bacteriophage specific to a target bacterium infect target bacteria, allowing the bacteriophage to become amplified in the target bacteria, and detecting the amplified bacteriophage. If the bacteriophage is detectable, it must have been amplified in target bacteria that were present in the original sample. Miller teaches detecting bacteria using immobilized phage as a binding agent to immobilize target bacteria. Rees contains no motivation to use immobilized phage and Miller contains no motivation to detect progeny phage. Indeed, Miller teaches *away* from combining Miller with Rees, stating that in contrast to conventional bacteriophage-based bacterial detection methods that include "time-consuming cultivation steps and the bacteriophage-mediated lysis of the cells" (e.g., assays such as that described in Miller), Miller enables detection in minutes rather than hours or days (Miller, paragraph [0011]). Combining the immobilized phage of Miller with a conventional bacteriophage-based, time-consuming, cultivation-based bacterial detection assay *defeats* the objectives of Miller. Thus, one skilled in the art would have had no motivation to combine Rees and Miller as suggested in the Office Action.

Because one skilled in the art would have had no motivation to combine Rees and Miller as suggested in the Office Action, the Office Action fails to establish a proper *prima facie* case of obviousness. Applicants respectfully request that the rejection be withdrawn.

Applicants respectfully submit that claims 1-4, 6, and 9 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the rejection be withdrawn.

Claims 7 and 8 are patentable over Rees *et al.* in view of Miller *et al.*, further in view of Vafai

Claims 7 and 8 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Rees and Miller as applied to claims 1-4, 6, and 9, and further in view of Vafai (U.S. Patent 5,824,319). Applicants respectfully traverse.

Each of claims 7 and 8 depends, directly or indirectly, from claim 1. Therefore, remarks made above that refer to claim 1 apply equally to claims 7 and 8.

The teachings and deficiencies of the combination of Rees and Miller are described in the immediately preceding section. Vafai is cited for teaching immunoassays in which an antibody is conjugated to a fluorescent dye. Consequently, Vafai fails to cure the deficiencies of the combination of Rees and Miller. Applicants therefore submit that claims 7 and 8 are patentable over the combination of Rees, Miller, and Vafai.

Applicants respectfully submit that claims 7 and 8 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the rejection be withdrawn.

Claims 13 and 14 are patentable over Rees *et al.* in view of Miller *et al.*, further in view of Vonk

Original claims 13 and 14 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Rees and Miller as applied to claims 1-4, 6, and 9, and further in view of Vonk *et al.* (*J. Immunol. Methods*, 137:133-139, hereinafter "Vonk"). These claims have been replaced by new claims 22- 25 and 27-28. Applicants respectfully traverse.

Claim 22 recites a method of detecting a bacterial cell in a sample. Claims 23–25 and 27-28 depend from claim 22 and, therefore, includes all of the features recited in claim 22. Thus remarks that refer to claim 22 apply equally to claims 23-25 and 27-28. Claim 22 recites, in part:

> removing the bacteriophage comprising a binding agent immobilized on a substrate from the sample;
>
> contacting the sample with a second substrate comprising immobilized binding agent specific for the new bacteriophage, under conditions effective for a complex to form between the new bacteriophage and the second substrate comprising immobilized binding agent for the new bacteriophage; and
>
> detecting the complexes of new bacteriophage and second substrate comprising immobilized binding agent for the new bacteriophage, wherein the presence of complexes of new bacteriophage and second substrate comprising immobilized binding agent for the new bacteriophage indicates the presence of a bacterial cell specific for the bacteriophage in the sample and wherein the absence of complexes of new bacteriophage

and second substrate comprising immobilized binding agent for the new bacteriophage indicates the absence of a bacterial cell specific for the bacteriophage in the sample.

Thus, claim 22 includes removing the bacteriophage comprising a binding agent immobilized on a substrate from the sample, which is neither taught nor suggested by the combination of Rees and Miller. Claim 22 further includes immobilizing the progeny phage for detection.

Vonk is said to teach the use of magnetic beads having antibodies against a virus attached thereto. The beads are incubated with a sample that includes the virus that is bound by the antibodies. The virus-binding beads are removed from the sample and assayed for the presence of the virus.

Thus, Vonk fails to cure the deficiencies of the combination of Rees and Miller regarding the removal of immobilized parent phage from the material subjected to the detection assay. Applicants therefore submit that claims 22 – 25 and 27-28 are patentable over the combination of Rees, Miller, and Vonk.

Applicants respectfully submit that claims 22 – 25 and 27-28 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the rejection be withdrawn.

Claims 5 and 15 are patentable over Rees in view of Miller and Vonk, and further in view of Sun *et al.*

Claims 5 and 15 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Rees and Miller as applied to claims 1-4, 6, and 9; or Rees and Miller in view of Vonk as applied to claims 13 and 14; and further in view of Sun et al. (*J. Indust Microbiol Biotechnol,* 25:273-275, hereinafter "Sun"). Claim 15 has been replaced by claim 26. Applicants respectfully traverse.

Claim 5 depends from claim 1 and claim 26 depends from claim 22. Thus, remarks made above regarding the patentability of claim 1 apply equally to claim 5. Similarly, remarks made above that refer to claim 22 apply equally to claim 26.

Sun is cited for teaching immobilizing phage though biotinylation. Consequently, Sun fails to cure the deficiencies of the combination of Rees and Miller (with respect to claim 1) and the combination of Rees, Miller, and Vonk (with respect to claim 22). Applicants therefore submit that claim 5 is patentable over the combination of Rees, Miller, and Sun. Applicants further submit that claim 26 is patentable over the combination of Rees, Miller, Vonk, and Sun.

Applicants respectfully submit that claims 5 and 26 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the rejection be withdrawn.

Claims 16 and 17 are patentable over Wilson in view of Olsvik *et al.*, Sun *et al.*, and Vonk

Claims 16 and 17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Wilson (U.S. Patent 5,985,596) in view of Olsvik et al. (*Clin. Microbiol. Rev.* 7:43-54, hereinafter "Olsvik"), Sun, or Vonk. These claims have been replaced by new claims 29-31 Applicants respectfully traverse.

Applicants respectfully submit that the Office Action fails to set forth a *prima facie* case of obviousness because, at least, the combination of Wilson in view of Olsvik, Sun, or Vonk ("the suggested combination") fails to set forth each and every feature recited in claim 29. Moreover, one skilled in the art would have had no motivation to combine the documents as suggested in the Office Action. Finally, the suggested combination of documents fails to provide one skilled in the art with a reasonable expectation that, by following the combined teachings of the documents, one could successfully practice the methods recited in claims 29-31.

Claim 29 is independent. It recites, in part, "...incubating the sample under conditions effective for the *bacteriophage comprising a binding agent* to infect the bacterial cell[.]" (emphasis added). Applicants respectfully submit that the suggested combinations of documents fail to teach or suggest incubating the sample under conditions effective for bacteriophage that comprises a binding agent to infect a bacterial cell.

Wilson teaches a method of detecting bacteria that involves allowing bacteriophage to infect a bacterium permissive to infection by the bacteriophage (see Abstract). Wilson fails to teach or suggest modifying the bacteriophage to include a binding agent. Wilson further fails to teach or suggest that a bacteriophage can be modified to include a binding agent and still retain the ability to infect a permissive bacterium. Also, the Office Acknowledges that Wilson fails to teach or suggest removing the first bacteriophage from the sample (Office Action, page 9).

None of Olsvik, Sun, or Vonk ("the secondary documents") teaches or suggests incubating a sample under conditions effective for the *bacteriophage comprising a binding agent* to infect the bacterial cell. The Office Action cites portions of Olsvik, Sun, and Vonk for teaching of certain separation techniques that can be used to detect and/or separate compounds (e.g., including viruses) from suspension. The Office Action argues it would have been obvious to modify the method of Wilson by removing the first population of bacteriophage using one of the separation techniques described in Olsvik, Sun, or Vonk.

This analysis ignores a feature recited in claims 29-31: the bacteriophage comprising a binding agent retains infection functionality. As applied in the rejection of claims 29-31, each of the secondary documents is directed toward mere detection and/or separation of viruses. None is concerned with maintaining biological functionality of the detected or separated viruses. Accordingly, none teaches or suggests modifying a virus for detection and/or separation in a manner that permits the viruses to infect a target cell.

Because the suggested combinations of documents fail to teach or suggest a bacteriophage comprising a binding agent being capable of infecting a bacterial cell, the suggested combinations fail to set forth each and every feature recited in claims 29-31. Therefore, the suggested combinations fail to set forth a *prima facie* case of obviousness.

Applicants further submit that the suggested combinations fail to motivate one skilled in the art to modify the teachings of Wilson in such a way as to arrive at the subject matter recited in claims 29-31. As noted above, each of the secondary documents, as applied to the rejection of claims 29-31, is directed toward mere detection and/or separation of viruses. None is concerned with maintaining biological functionality of the detected or separated viruses. Thus, the Office Action has failed to establish why one skilled in the art would have looked to modify the viruses in the method of Wilson to include a binding agent *prior to* allowing the viruses to infect the target cells.

Because the suggested combinations of documents fail to provide motivation to one skilled in the art to modify bacteriophage to include a binding agent *prior to* being allowed to infect a bacterial cell, the suggested combinations fail to set forth a *prima facie* case of obviousness.

Applicants further submit that the secondary references, when combined with Wilson, fail to provide one skilled in the art with a reasonable expectation of successfully forming a bacteriophage that includes a binding agent *and* remains capable of infecting a bacterial cell. The combined teachings of the suggested combinations fail to enable one skilled in the art to make a bacteriophage modified to include a binding agent that is capable of being used in the methods recited in claims 29-31.

Because the suggested combinations of documents fail to provide one skilled in the art a reasonable expectation of successfully modifying bacteriophage to include a binding agent *and* retain the ability to infect target bacteria, the suggested combinations fail to set forth a *prima facie* case of obviousness.

Applicants respectfully submit that claims 29-31 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the rejection be withdrawn.

Summary

It is respectfully submitted that the pending claims 1-9 and 20-47 are in condition for allowance and notification to that effect is respectfully requested. An RCE and a request for a one month extension of time are enclosed along with the required fees. No additional fee is seen to be required. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted
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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to **Mail Stop RCE**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450,
on this 11 day of Sept, 2007, at 5:00 p.m. (Central Time).

By: Sandy Truehart
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